

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Liew et al.	Art Unit:	3737
Appl. No:	10/753,976	Examiner:	Ramirez, J.
File Date:	January 7, 2004	Docket No.:	3155/121
Confirmation:	6434		
Invention:	<b>METHODS OF PREDICTING MUSCULOSKELETAL DISEASE</b>		

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**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Dear Sir:

Following a Final Office Action dated December 7, 2006, and an Advisory Action dated March 28, 2007, Applicants submit the present Request for Formal Review, by a panel of examiners, of the legal and factual basis of the rejections pending in the present case, in accordance with the Pre-Appeal Brief Conference Pilot Program<sup>1</sup>. Applicants believe that the issues presented are well-posed for appeal, and request formal review prior to appeal on the following grounds:

**I. Background Synopsis of Subject Matter**

The present application relates to methods of predicting bone or joint diseases in a subject and methods of determining the effect of a candidate agent on any subject's risk of developing bone disease. The method of predicting bone or joint diseases in a subject determines micro-structural, macroanatomical, and biomechanical parameters by extracting information from an image of the subject. The method then combines at least two of the parameters to predict the risk of bone or articular disease. The parameters combined must include two or more of the micro-structural, macroanatomical, and biomechanical parameters.

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<sup>1</sup> Official Gazette of the United States Patent and Trademark Office, vol. 1296, Number 2, (July 12, 2005).

## **II. Synopsis of Status of the Case**

Claims 1-21 are pending in the application. In the Final Office Action of December 7, 2006, Claims 1, 2, 6, 7, 9-11, and 13 were rejected under 35 U.S.C. 102(b) as being anticipated by Wherli et al., U.S. Patent No. 5,247,934. Additionally, claims 3-5, 8, 12, 20, and 21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wherli in view of Mazess, U.S. Patent No. 5,673,298, in further view of Arnold, U.S. Patent No. 5,335,260, and further in view of Paul et al., U.S. Patent No. 5,320,102. Lastly, claims 14-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wherli et al., in view of Pak et al., U.S. Patent No. 5,228,445.

A response to the Final Office Action was filed on February 5, 2006 in which the Applicants explained that the Wherli reference does not teach or suggest the determinations and combinations carried out by the present invention. Specifically, Applicants argued that Wherli discloses a method of diagnosing osteoporosis based solely on trabecular microstructure, and that Wherli does not measure nor diagnose based on macroanatomical or biomechanical parameters.

Applicants received a Final Advisory Action dated March 28, 2007 in which the Examiner disagreed with Applicants arguments and stated that the response did not place the application in condition for allowance. The appeal, noticed concurrently herewith, is with respect to rejected claims 1-21.

## **III. Issues for Review Prior to Appeal**

### **I. A *prima facie* anticipation or obviousness rejection is improper when claim limitations are not found in the cited prior art reference(s).**

It is well settled that a claim is invalid as anticipated under 35 U.S.C. § 102 only if a single prior art reference discloses either expressly or inherently, each limitation of the claim. *In re Cruciferous Sprout Litigation*, 301 F.3d 1343, 64 U.S.P.Q. 2d 1202 (Fed. Cir. 2002). Additionally, as set forth in MPEP §§ 2143 and 2143.03, the cited prior art references must teach or suggest all claim limitations before a *prima facie* case of obviousness can be made. Wherli et al. simply does not disclose each and every

limitation of the present claims, alone or in combination with Mazess, Arnold, Paul, and Pak.

As mentioned above, the claims define a method of predicting bone or articular disease that includes determining one or more micro-structural parameters, and one or more macroanatomical parameters or biomechanical parameters of a joint. The method then combines at least two of the parameters (including two or more of a micro-structural parameter, a macro-anatomical parameter, and a biomechanical parameter) to predict the risk of bone or articular disease.

The present application provides a definition of the term “micro-structural parameter” by stating that the terms micro-structural parameters, micro-architecture, micro-anatomical structure, micro-structural and trabecular architecture may be used interchangeably (see page 7, paragraph 54 of the U.S. Patent Application Publication US2004/0242987). Werli also classifies trabecular structure as a “micromorphometric” parameter. Specifically, at column 6, lines 45-50, Werli states that microscopic NMR images can be useful in measuring “micromorphometric parameters, such as bone volume, trabecular thickness, intercept length, and fabric tensor.” Accordingly, trabecular structures and characteristics are considered micro-structural parameters within the present application, as well as in the Werli reference. Therefore, any measurement carried out by Werli that is related to any trabecular structure or parameters are micro-structural, rather than macroanatomical (e.g., such as the overall geometry of the bone, the length of the neck, diameter of the femoral head, thickness of the cortical bone, etc.), or biomechanical.

The purpose and intent of Werli is to characterize and quantify *trabecular* bone with nuclear magnetic resonance imaging (see col. 1, line 5-12; col. 10, lines 56-61). Specifically, Werli discloses a method of diagnosing osteoporosis based solely on trabecular *microstructure* (see col. 3, lines 33-42; col. 4, lines 23-31; col. 9, lines 53-56; col. 10, lines 56-61). As mentioned above, trabecular structure and characteristics are micro-structural parameters, not macroanatomical or biomechanical parameters. Therefore, nowhere does Werli disclose predicting disease based on two or more of a micro-structural parameter, a macroanatomical parameter, and a biomechanical parameter, as required by the present claims.

In the Advisory Action dated March 28, 2007, the Examiner seems to indicate that Figures 1, 2, and 4 of Wherli disclose the use of parameters other than micro-structural parameters. However, this is simply not the case. As discussed at column 7, lines 26-41 of Wherli, Figure 1 shows a region of interest (ROI) superimposed on *trabeculae* surrounded by bone marrow. As mentioned above, trabeculae are micro-structural parameters, not a macroanatomical or biomechanical parameters. Additionally, as mentioned above, Wherli also classifies the intercept length (shown in Figure 1) as micro-structural.

Further, the images used by Wherli only include trabecular bone and not bone on a macroanatomical scale. As mentioned above, Wherli deals with a region of interest that is trabeculae surrounded by bone marrow. Anatomically, such an area of interest can only include trabecular bone because trabecular bone is the only bone located in and around the bone marrow. Therefore, the Wherli's method can only includes microstructural parameters because the images and ROI used by Wherli do not include macroanatomical parameters.

Lastly, the Wherli methodology is, in fact, incapable of determining macro-anatomical parameters, as required by the pending claims. All of the methodologies and examples presented by Wherli utilize microscopic NMR image or other microscopy techniques to measure the parameters used by Wherli to diagnose osteoporosis. By definition, microscopic NMR and microscopy are looking at microstructure, not macrostructure. Therefore, any measurements obtained must also be microstructural.

The Mazess, Arnold, Paul, and Pak references also do not teach or suggest using macro-anatomical and/or biomechanical parameters to predict musculoskeletal disease as required by claims 1-21. Mazess discloses a method for automatically analyzing the morphometry of bones from data obtained by lateral scans of the bone. Mazess then calculates indicia of bone condition such as length or spacing and compares these indicia to a set of reference values. Nowhere does Mazess disclose extracting trabecular micro-structure from an image. Nor does Mazess disclose determining one or more micro-structural parameters, one or more macroanatomical parameters or biomechanical parameters of a joint, and combining these parameters to predict disease, as required by the claims.

The Arnold reference merely discloses a calibration phantom and discusses how to use the calibration phantom to quantify bone mineral density of a patient. Nowhere does Arnold disclose determining one or more micro-structural parameters, one or more macroanatomical parameters or biomechanical parameters of a joint, and combining these parameters to predict disease, as required by the claims.

The Paul reference discloses a method for non-invasively diagnosing proteoglycan deficiencies in articular cartilage. The Paul method quantifies a signal intensity of an MRI image and correlates the intensity with a reference signal intensity. Nowhere does Paul disclose extracting trabecular micro-structure from an image. Nor does Paul disclose determining one or more micro-structural parameters, one or more macroanatomical parameters or biomechanical parameters of a joint, and combining these parameters to predict disease, as required by the claims.

The Pak reference discloses a treatment process for improving the intrinsic quality of bone in osteoporotic patients by administering a form of sodium fluoride. Pak discusses using spine films to evaluate the treatment (col. 19, lines 31-54), however, Pak does not teach nor suggest predicting disease based on two or more of a micro-structural parameter, a macro-anatomical parameter, and a biomechanical parameter, as required by claims 14-19 (which depend on claim 1). Further, Pak does not teach nor suggest combining at least two of these parameters to predict the risk of disease.

Applicants therefore submit that claims 1-21 are patentable over Wherli alone and in combination with Mazess, Arnold, Paul, and Pak. Allowance of claims 1-21 is respectfully requested.

Respectfully submitted,

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